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A home-mailed versus general practitioner-delivered vaginal self-sampling kit for cervical cancer screening: a cluster randomized controlled trial with a cost-effectiveness analysis

Vaginal self-sampling in cervical cancer screening

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Keywords: cervical cancer screening; self-sampling; HPV; unscreened women; general practitioner; delivery

Abbreviations: CCS: cervical cancer screening, GP: general practitioner

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Abstract

Objective

We assessed whether general practitioner (GP) delivery of a vaginal self-sampling kit was non-inferior to home-mailed delivery on cervical cancer screening participation.

Methods

Two hundred and ten French GPs from Indre-et-Loire French department were randomized into two groups and their unscreened women patients aged 30-65 were included in February-March 2015. In the GP delivery group (n=105 GPs; 1806 women), women were sent a reminder letter inviting them to collect a vaginal self-sampling kit at their regular GP's practice. In the home-mailed delivery group (n=105 GPs; 1806 women), women were sent a reminder letter with a vaginal self-sampling kit directly at home. The primary outcome was participation in complete cervical cancer screening within 9 months. A cost-effectiveness analysis was also performed.

Results

At 9 months, 14.9% (95% CI, 12.9 to 16.9) and 27.9% (95% CI, 25.7 to 30.0) of women in the GP and home-mailed delivery groups participated in complete cervical cancer screening. The absolute between-group difference was -13.0 percentage points (95% CI, -15.9 to -10.0) in favor of the home-mailed delivery group, crossing the non-inferiority pre-defined non-inferiority margin of 5%. The home-mailed delivery strategy costed 50.81€ more per additional woman screened.

Conclusions

GP delivery was inferior to home-mailed delivery in increasing participation in cervical cancer screening. Home-mailed delivery of a vaginal self-sampling kit is a cost-effective way to increase cervical cancer screening in that the additional cost of this strategy seems acceptable.

Trial registration

This study is registered at www.Clinicaltrials.gov NCT02255084.

Introduction

Cervical cancer is the third female cancer worldwide, with 569 847 estimated new cases and 311 365 deaths in 2018.¹ In mainland France, 2920 new cases and 1120 deaths from cervical cancer were estimated in 2018.² Organized cervical cancer screening programs based on Papanicolaou cytology (Pap smear) have shown their efficiency in reducing cervical cancer incidence and mortality in most developed countries.³

When the study took place, France had no national cervical cancer screening (CCS) program, but 9 regions had a pilot program (based on Pap smear, as HPV test was not yet recommended in France at this time). During 2010-2012, the screening coverage was 62.3% over those 9 areas and 60.5% in Indre-et-Loire French department,² far from the national objective of 80%.⁴ Because most cervical cancers occur in unscreened women,⁵ we need complementary strategies to reach these women.⁶

Persistent infection with high-risk papillomavirus (HR-HPV) is the necessary risk factor for cervical cancer.^{7,8} For women 30 to 65 years old, HR-HPV-based tests are more sensitive to detect cervical intra-epithelial neoplasia grade 2–positive (CIN2+) lesions than is Pap smear, and the screening interval could be extended to 5 years for HR-HPV-negative women.⁹ Using the HR-HPV-based test as a primary screening test opens the possibility of self-sampling. By offering an in-home test performed by women themselves, many adherence barriers to that screening could be lifted. HR-HPV tests of vaginal self-sampling with a PCR step show similar sensitivity as clinician sampling to detect CIN2+ lesions.¹⁰

Several randomized controlled trials have shown greater participation when using a vaginal self-sampling kit mailed to unscreened women as compared with sending an invitation for a screening test performed by a health professional, whatever the self-sample device and the setting of the trial (pooled relative participation in intent-to-treat-analysis of 2.33, 95% confidence interval [CI] 1.86 to 2.91).¹¹ Offering a self-sampling kit to unscreened women could increase CCS coverage, but its weaknesses are lack of contact with a health professional and wasted resources.

The APACHE-3 trial aimed at assessing the noninferiority of general practitioner (GP) delivery as compared with home-mailed delivery of a vaginal self-sampling kit on CCS participation. As the cost of GP delivery is expected to be lower, a cost-effectiveness analysis was also performed to assess the efficiency of this strategy.

Methods

Study Design

The APACHE-3 trial was a noninferiority two-parallel-group cluster randomized controlled trial. Randomization units were GPs from the Indre-et-Loire French department. A cluster design was chosen for logistical and economic considerations and to avoid contamination within general practices.

The study protocol was approved by the local ethics committee (n°2014-R30) and a waiver of individual participant-level informed consent was granted.

Settings and participants

The present study took place in the Indre-et-Loire French department where about 160 000 women are targeted for CCS. In the regional program, unscreened women aged from 25 to 65 years old are routinely identified by crossing information from different sources: target population file and Pap smear reimbursement data from health insurance organizations and the major part (approximately 90%) of Pap smear results from pathologists' labs. By crossing the different sources of information, we considered data on screening status were almost exhaustive. Unscreened women (no Pap smear in the past 3 years) receive an invitation letter from the Cancer Screening Department to have a Pap smear performed by their GP, gynecologist or midwife. Nine months later, in the absence of Pap smear data, a reminder letter is sent.

Eligible women were 30 to 65 years old who declared one of the randomized GPs as referring GP and did not have a Pap smear within 9 months after an invitation letter. We included all women meeting first the inclusion criteria between February and March 2015 until reaching the target sample size of 3612 women. The number of selected women could thus vary across the GPs.

Randomization and masking

The whole trial process with blinding at each step is described in Figure 1.¹² In October 2014, a random sample of 210 among the 527 GPs registered in the Indre-et-Loire area was included in the trial. There were no specific eligibility criteria for GPs. These 210 GPs were randomized with a 1:1 ratio to GP delivery or home-mailed delivery group. To avoid contamination, GPs practicing within the same medical practice were allocated to the same group. The allocation sequence was computer-generated and stratified on the practice size according to five strata (practices with 1, 2, 3, 4 or > 4 GPs) by a statistician not further involved in the study.

The selection of women was handled by an independent computer programming company that is in charge of the screening program management software routinely used in the Cancer Screening Department (Zeus, OsiSanté, Thury-Harcourt, France) and which was not further involved in the study.

Owing to the nature of the intervention, GPs in the GP delivery group and women in both groups were aware of their group allocation but they were not aware of the study hypotheses.

The women were not aware of the alternative intervention. Moreover, risk of bias was limited by the fact that the primary outcome was collected from routinely collected data and laboratory results measured by a blinded staff.

Interventions

Before the start of the trial, every GP and gynecologist practicing in the Indre-et-Loire region received a letter to inform them about the two delivery strategies, to sensitize them about vaginal self-sampling and to let them know they could receive results letters for their patients.

In the GP delivery group, GPs were provided with 15 vaginal self-sampling kits, instructions for their delivery and a copy of the letter that would be sent to included women. Eligible women received a reminder letter inviting them to consult their referring GP to collect a vaginal self-sampling kit. They were asked to use the kit at home.

In the home-mailed delivery group, GPs received no further information. Eligible women received a reminder letter with a vaginal self-sampling kit directly at home.

In both groups, the vaginal self-sampling kit consisted of 1) a leaflet explaining how to perform the vaginal self-sampling (see appendix), 2) a validated nylon flocked swab in a non-breakable dry sterile tube (52980C, Copan, Brescia, Italy),^{13,14} 3) a resealable plastic bag, 4) an identification sheet and 5) a pre-stamped, pre-addressed envelope to return the self-sampling to a centralized laboratory (Virology Laboratory of the University Hospital of Tours, France) for HR-HPV testing.

In both groups, women could opt for a pap smear instead of self-sampling.

Practical course

Definition of success and failure of the screening procedures were standardized (Figure S1).

In case of a second uninterpretable HR-HPV test result, women were advised by phone to have a Pap smear. Women with negative HR-HPV test results were advised to have a Pap smear 3 years later. Women with positive HR-HPV test results, were recommended to have a triage Pap smear within 3 months; they were re-contacted at 3 and 6 months after the HR-HPV results if the Pap smear was not performed within the time limit. In case of abnormal results, follow-up data were collected according to the French guidelines.¹⁵

Laboratory testing

The self-sampling device was first eluted in an adapted buffer (Abbott Cervi Collect specimen collection kit). HR-HPV detection was performed in a centralized laboratory (Virology Laboratory of the University Hospital of Tours, France) with a real-time PCR-based assay (Abbott RealTime High Risk HPV).^{16,17} This assay is intended to detect 14 HR-HPV genotypes — 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68 — and to genotype specifically type 16 and 18. An endogenous human beta globin sequence is detected as a sample validity control for cell adequacy, sample extraction and amplification efficiency. In case of negativity for this control, a diluted sample was analyzed to exclude the presence of inhibitors. If the second test was negative for this internal control, the test result was considered uninterpretable. HR-HPV results were classified as positive for HR-HPV when at

least one HR-HPV genotype was detected and negative when no HR-HPV genotype was detected. Pap smears were evaluated in cytology laboratories according to usual practices. Laboratory tests were performed by staff with blinding to group.

Outcome measurement

The primary outcome was the woman's participation in complete CCS within 9 months after the reminder letter. In both groups, participation in complete screening was defined as having a Pap smear or performing the self-sampling, completed by a triage Pap smear in case of positive results (within 9 months after the HPV results) (Figure S1).

Secondary outcomes were 1) participation in complete CCS via vaginal self-sampling within 9 months after the reminder letter and 2) participation in complete CCS with a Pap smear within 9 months after the reminder letter.

Cytology (Pap smear) and histology (biopsy) results were extracted from routinely collected data from the Cancer Screening Department database. Pap smear results were classified by the 2014 Bethesda system.¹⁸ Histology results were classified as normal, CIN1, CIN2, CIN3 or cancer.

Data collection

Baseline characteristics for patients, GPs and practices were extracted from the Cancer Screening Department database. HR-HPV test and Pap smear results were extracted from routinely collected data from the Cancer Screening Department database.

Statistical analysis

On the basis of results from a previous trial,¹⁴ we assumed a 20% participation in complete cervical screening percentage in both groups. The noninferiority margin was fixed at 5%. Considering a power of 90% and a two-sided alpha of 5%, we needed 1350 women per group. We applied a variance inflation factor because clusters (i.e., GPs) and not participants were randomized. By using the Cancer Screening Department database, we estimated an average number of eligible women per GP of 17.2, with a coefficient of variation of 0.9. The inflation factor was calculated with the Eldridge et al. approach:¹⁹ this factor is defined by $1 + [(CV^2 + 1) m - 1] \rho$, where CV is the coefficient of variation associated with the size of the clusters, m is the average cluster size and ρ is the intraclass correlation coefficient (ICC). Considering an ICC of 0.01 (this value was chosen according to the nature of the primary outcome, which is an "outcome" variable as opposed to a "process" variable, reflecting an individual choice, probably moderately affected by the cluster effect), the inflation factor was 1.30, leading to a sample size of 1755 women per group. We planned to include 105 GPs, each associated with 17.2 women, on average, for 1806 women needed per group.

The aim of the trial was first to assess the non-inferiority of GP delivery versus home-mailed delivery and in case non-inferiority was shown a second analysis would determine whether

GP delivery was superior to home-mailed delivery (switch to superiority objective). Each analysis was planned to be tested at a one-sided type I error of 2.5%.²⁰

The primary analysis was performed at the individual level, according to the intention-to-screen principle. GPs who changed their practice after randomization (practice cessation, address modification) were excluded from the analysis. For the primary outcome, percentages were reported with their 95% CIs. The estimation of the two-sided 95% CI from the between-group difference in participation percentages involved using a normal approximation.

Variances were adjusted for clustering at the GP level by using a ratio-estimator approach.

Noninferiority would be declared if the lower boundary of the 95% CI of the between-group difference in the percentage of women with complete CCS (percentage in the GP delivery group minus percentage in the home-mailed delivery group) was not less than -5 percentage points. The same approach was used for secondary outcomes. Pre-specified subgroup analysis (age <50 vs \geq 50 years old) involved using a mixed logistic regression model with intervention group, subgroup and group*subgroup interaction as fixed effects and cluster as a random effect. ICCs were estimated with the Fleiss and Cuzick estimator in each group with their 95% CIs obtained with the Zou and Donner method,²¹ with values truncated to zero in case of negative estimation. Analyses involved using SAS v 9.4 (SAS Institute Inc., Cary, NC, USA).

Health-economic evaluation

Cost-effectiveness analysis involved using TreeAge 2017 software, modelling the women's pathway in a decision tree based on observed data from the APACHE 3 study. Effectiveness data corresponded to the primary outcome (success or failure). Direct medical costs arising between randomization and evaluation of the primary outcome were included in the analysis.

For both groups, costs considered in the analysis were : costs for the different reminder letters (stationery, printing, labor required to prepare the mailing and postage) according to the groups; costs of postal return of self-sample to laboratory ; costs of laboratory analysis (HR-HPV test) and mailing tests results ; in case of uninterpretable result, costs for sending a second vaginal self-sampling kit ; costs of reminder letters and phone calls after a positive HR-HPV result on the vaginal self-sampling without triage Pap smear, costs of consultation to perform a Pap smear (GP, midwife or gynecologist) including potential extra fees and costs of Pap smear analysis (cytology analysis) and result sending. In the home-mailed delivery group, the cost of a vaginal self-sampling kit was considered for each reminder. In the GP delivery group, specific costs considered were: GP's consultation, vaginal self-sampling kit and the sending of this kit to GP. All these costs are detailed in the Table S2. Costs have been valued from a societal point of view (i.e., costs covered by health insurance, Cancer Screening Department and women). No discounting was applied.

Mean cost per woman and cost-effectiveness ratios were calculated for each group. The incremental cost-effectiveness ratio (ICER) per extra screened woman was calculated by dividing the between-strategy mean cost per woman difference by the between-strategy rate of screened women at 9 months. One-way and deterministic sensitivity analyses were performed to evaluate the extent to which the uncertainty in effect and cost data would change the ICER.

Results

GPs and Participants

Among the 210 randomized GPs (Figure 2), 4 GPs in the GP delivery group and one in the home-mailed delivery group had stopped their activity (retired or changed practice) before the inclusion of women. One GP in the home-mailed delivery group had no eligible patient. From February to March 2015, 3612 women, patients of the randomized GPs, were included in the study (1806 in each group). The mean (standard deviation) age of included women was 50.6 years (11.2) and 48.9 years (11.1), respectively.

Study conduct

In the GP delivery group, 2 women had an uninterpretable HPV test result; one performed a second self-sampling. In the GP delivery group, some GPs gave the self-sampling kit to women not included in the study. In that case, the self-samplings were not analyzed by the centralized laboratory. Those women were advised by the Cancer Screening Department staff to have a Pap smear performed by a health-care provider. GPs in this group received phone calls and reminder letter about delivery conditions.

Participation in complete CCS

In the GP delivery group, 269 of the 1806 women (14.9%) participated in complete CCS within 9 months versus 503 of the 1806 women (27.9%) in the home-mailed delivery group (Figure 2 and Table 1). The absolute risk difference was -13.0 percentage points (95% CI, -15.9 to -10.0): the lower boundary was smaller than the prespecified -5 percentage-point non-

inferiority margin. Thus, the non-inferiority of GP delivery was not met. Although the trial was intended to assess the non-inferiority of GP delivery over the home-mailed delivery, our findings demonstrated that participation in complete CCS was significantly lower with GP delivery than with home-mailed delivery ($p \leq 0.001$).

Participation in complete CCS was mostly achieved by the use of Pap smear in the GP delivery group. Among the 269 women with complete CCS, 48 (17.8%) used self-sampling and 221 (82.2%) a Pap smear performed by a health professional. However, in the home-mailed delivery group, among 503 women with complete CCS, 314 (62.4%) used self-sampling and 189 (37.6%) a Pap smear performed by a health professional.

Participation in complete CCS by self-sampling was significantly lower in the GP delivery group as compared to the home-mailed group (2.7% vs. 17.4%; $p < 0.001$; Table 1).

Participation in complete CCS by the use of Pap smear did not differ between groups (12.2% vs. 10.5%; $p = 0.13$).

Subgroup analysis according to age (35-49 vs 50-65 years) consistently favored home-mailed delivery ($p_{\text{interaction}} = 0.2831$) (Figure S2).

Test results and women's follow-up

In the GP delivery group, 49 women performed self-sampling within 9 months, and 48 test results were interpretable, with 4 (8.3%) samples positive for HR-HPV (Figure 2); the 4

women underwent the recommended triage Pap smear. A Pap smear test result was available for the 4 samples, and 1 was abnormal (25% of known results) (Table S1).

In the home-mailed delivery group, 316 women performed self-sampling within 9 months, and 315 test results were interpretable, with 47 samples (14.9%) positive for HR-HPV; 46 (97.9%) of these women underwent the recommended triage Pap smear. A Pap smear test result was available for 44 of 46 samples, and 5 (11.4% of known results) were abnormal (Table S1).

Finally, among women who participated in complete CCS at 9 months after the reminder letter, 4 had CIN2 cancer or worse: 1 CIN3 in the GP delivery group among women who had a Pap smear, 1 CIN2 in the GP delivery group among HR-HPV-positive women, 1 CIN2 in the home-mailed delivery group among women who had a Pap smear, and 1 CIN3 in the home-mailed delivery group among HR-HPV-positive women. In both groups, the CIN2+ detection rate among included women was 1.1%.

Cost-effectiveness analysis

The mean cost per woman included was higher in the home-mailed than GP delivery group (15.60€ vs 9.01€) (Table 2). Nevertheless, the cost-effectiveness ratio favored the home-mailed delivery group (56.00€ vs 60.52€) (Table 2). As compared with the GP delivery strategy, with the home-mailed delivery strategy, the gain in effectiveness generated an additional cost (ICER) of 50.81€ per extra screened woman. Costs of resources engaged per screened women for each intervention group are detailed in Table S2.

Regarding the sensitivity analyses (Table S3), the variable most affecting the ICER was the cost of home-mailed delivery. If this cost was 5€ instead of 1.559€, the ICER would be 77.36€ per extra screened woman. A 50% reduction in the cost of HR-HPV test analysis and mailing results (20.00€ instead of 37.80€) and a doubling of the probability of returning the test within 9 months in the GP delivery group (5.43% instead of 2.71%) would decrease the ICER (30.57€ and 45.93€). The other variables did not significantly affect the ICER.

Discussion

In a large sample of 3,612 women, we did not show the non-inferiority of GP delivery of a vaginal self-sampling kit and conversely, we found that participation in complete CCS was significantly higher in the home-mailed group. The substantial increase in participation with the home-mailed delivery strategy offset its higher mean cost, leading in a lower cost-effectiveness ratio as compared with the GP delivery strategy. Sending a kit directly to the home so that the women can take the sample themselves improved adherence to CCS.

Our study is the first to compare home-mailed delivery versus the delivery by the GP. In Italy, a similar trial assessed delivery by another health professional, the pharmacist. As for our study, participation was almost halved as compared with directly mailing the self-sampling kit to the women's home (21.6% vs 11.9%).²² This lower participation rate with health professional delivery could have several explanations. This strategy requires an additional step that consisted, in our study, of making an appointment with a GP. Women may have felt embarrassed by this type of proposal or the autonomy offered by the kit may have frightened some of them, especially without seeing it. It would have been interesting to do subgroup analyses according to socioeconomic status and educational levels, but such information is not part of the Cancer Screening Department database. In addition, health professionals may not have been well informed about this new type of sampling.

Owing to the higher participation rate with the home-mailed than GP delivery strategy, the cost-effectiveness ratio was lower with the former strategy. Numerous studies have shown that offering a self-sampling kit to under-screened women is an effective or cost-effective strategy under certain conditions.²³ In our study, the home-mailed delivery strategy was more

expensive, with an ICER of about 50€ per extra screened woman as compared with the GP delivery strategy. However, the final ICER for the home-mailed versus GP delivery strategy depends on the total number of women targeted and the expected success rate of the strategy. To reduce this additional cost while maintaining the increased participation, the cost of the HR-HPV test must be reduced while ensuring that the cost of the vaginal self-sampling kit remains low.

Since the end of our study, many high-income countries, including France, have switched to or are in the process of switching to first-line HR-HPV testing. Some countries such as The Netherlands²⁴ and Australia²⁵ have already included home mailed self-sampling kits as an option in their national screening programs. The French authorities recommended in 2019 to switch from the Pap smear to the HR-HPV test for women aged 30 to 65 and to offer the vaginal self-sampling kit to under-screened women.²⁶ At the same time, the national CCS program has been set up in France. For future implementation of self-sampling kits, the context will be more favorable. Communication with the health professionals and women will be strengthened. More strategies to improve the efficiency of the home delivery need to be explored: opt-in, on line ordering, SMS recall etc. Opt-in strategies (self-sampling kit sent on demand) have not been tested in France, and we lack sufficient studies to determine whether this strategy would be cost-effective.²³ In addition, it would be interesting to evaluate the GP delivery of vaginal self-sampling kit in an opportunistic approach. This kind of delivery experiment would require a study over a period of several years and a qualitative evaluation about GP workload and the obstacles faced by women may complement such approach.

In conclusion, we showed that GP delivery of a vaginal self-sampling kit resulted in significantly lower participation in complete CCS as compared with home delivery of the kit in France. Thus, offering a vaginal self-sampling kit could be an effective way to improve the CCS participation, but we cannot recommend the GP delivery strategy as implemented in our trial. More strategies based on self-sampling need to be evaluated to identify optimal and efficient strategies for national programs.

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399

400 **Author Contributions**

401 Boyard and Haguenoer had full access to all of the data in the study and take responsibility
402 for the integrity of the data and the accuracy of the data analysis.

403 Study concept and design: Boyard, Sengchanh, Giraudeau and Haguenoer.

404 Acquisition of data: Cancer Screening Department, Virology Laboratory.

405 Analysis and interpretation of data: Boyard, Caille, Brunet-Houdard, Sengchanh and
406 Haguenoer.

407 Drafting of the manuscript: Boyard, Caille, Brunet-Houdard, Gaudy-Graffin and Haguenoer.

408 Critical revision of the manuscript for important intellectual content: Boyard, Caille, Brunet-
409 Houdard, Giraudeau, Marret, Rusch, Gaudy-Graffin and Haguenoer.

410 Statistical analysis: Caille

411 Cost-effectiveness analysis: Brunet-Houdard.

412 Obtained funding: Boyard, Sengchanh, Giraudeau and Haguenoer.

413 Virology analysis: Gaudy-Graffin

414 Help with writing intervention letters: Rolland-Lozachmeur

415 Study supervision: Boyard, Sengchanh and Haguenoer.

416

417

418 **Conflict of Interest**

419 The authors declare that they have no known competing interests, personal financial interests,
420 funding or employment that may inappropriately influence or affect the integrity of the work
421 reported in this paper.

422

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426

427 **Data Availability**

428 Datasets are available from the corresponding author (subject to the applicable regulations:
429 General Data Protection Regulation). Data will be made available to researchers whose
430 proposed use of the data has been approved and with a signed data access agreement.

431 **References**

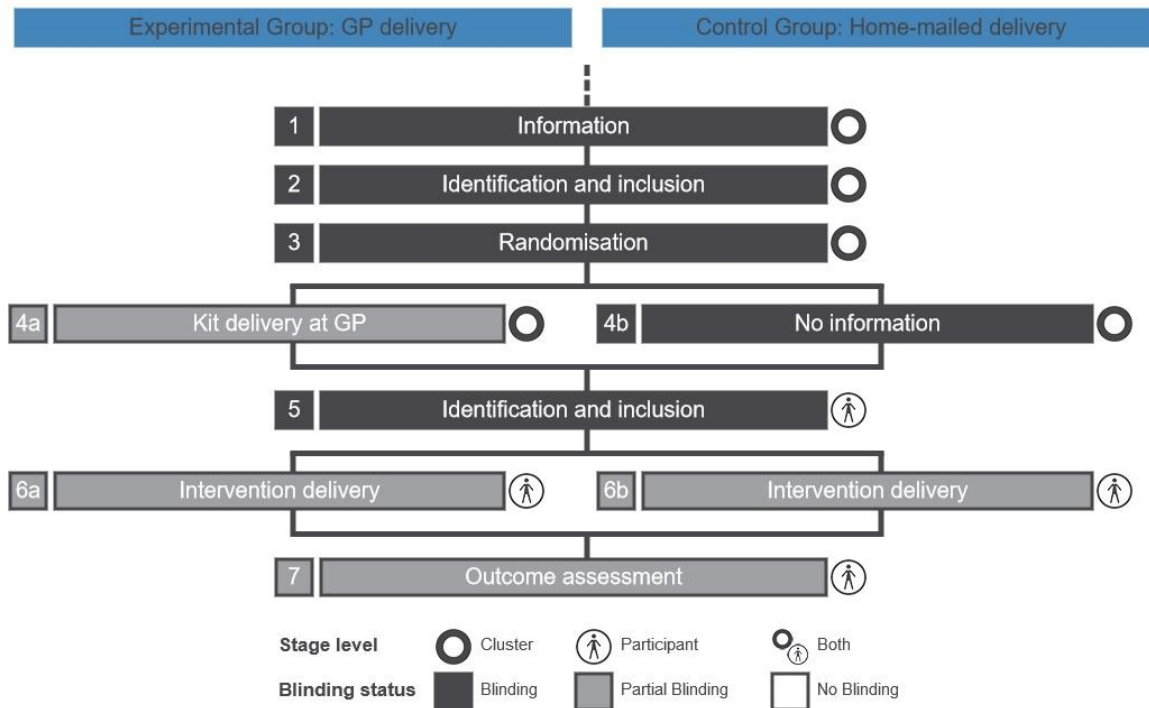
-
- 432 1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer
433 statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36
434 cancers in 185 countries. *CA Cancer J Clin.* 2018;68(6):394-424.
435 doi:10.3322/caac.21492
- 436 2. Hamers FF, Duport N, Beltzer N. Population-based organized cervical cancer screening
437 pilot program in France. *Eur J Cancer Prev Off J Eur Cancer Prev Organ ECP.*
438 2018;27(5):486-492. doi:10.1097/CEJ.0000000000000365
- 439 3. Arbyn M, Castellsagué X, de Sanjosé S, et al. Worldwide burden of cervical cancer in
440 2008. *Ann Oncol Off J Eur Soc Med Oncol ESMO.* Published online April 6, 2011.
441 doi:10.1093/annonc/mdr015
- 442 4. French National Authority for Health. [Assessment and recommendations for cervical
443 cancer screening in France]. Published online July 2010.
- 444 5. Zucchetto A, Ronco G, Giorgi Rossi P, et al. Screening patterns within organized
445 programs and survival of Italian women with invasive cervical cancer. *Prev Med.*
446 2013;57(3):220-226. doi:10.1016/j.ypmed.2013.05.018
- 447 6. Darquy S, Moutel G, Jullian O, Barré S, Duchange N. Towards equity in organised
448 cancer screening: the case of cervical cancer screening in France. *BMC Womens Health.*
449 2018;18(1):192. doi:10.1186/s12905-018-0683-0
- 450 7. Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary
451 cause of invasive cervical cancer worldwide. *J Pathol.* 1999;189(1):12-19.
452 doi:10.1002/(SICI)1096-9896(199909)189:1<12::AID-PATH431>3.0.CO;2-F
- 453 8. Muñoz N. Human papillomavirus and cancer: the epidemiological evidence. *J Clin Virol*
454 *Off Publ Pan Am Soc Clin Virol.* 2000;19(1-2):1-5.
- 455 9. Arbyn M, Ronco G, Anttila A, et al. Evidence regarding human papillomavirus testing in
456 secondary prevention of cervical cancer. *Vaccine.* 2012;30 Suppl 5:F88-99.
457 doi:10.1016/j.vaccine.2012.06.095
- 458 10. Arbyn M, Verdoodt F, Snijders PJF, et al. Accuracy of human papillomavirus testing on
459 self-collected versus clinician-collected samples: a meta-analysis. *Lancet Oncol.*
460 2014;15(2):172-183. doi:10.1016/S1470-2045(13)70570-9
- 461 11. Arbyn M, Smith SB, Temin S, Sultana F, Castle P, Collaboration on Self-Sampling and
462 HPV Testing. Detecting cervical precancer and reaching underscreened women by using
463 HPV testing on self samples: updated meta-analyses. *BMJ.* 2018;363:k4823.
464 doi:10.1136/bmj.k4823
- 465 12. Caille A, Kerry S, Tavernier E, Leyrat C, Eldridge S, Giraudeau B. Timeline cluster: a
466 graphical tool to identify risk of bias in cluster randomised trials. *BMJ.* 2016;354:i4291.
467 doi:10.1136/bmj.i4291

- 468 13. Haguenoer K, Giraudeau B, Gaudy-Graffin C, et al. Accuracy of dry vaginal self-
469 sampling for detecting high-risk human papillomavirus infection in cervical cancer
470 screening: A cross-sectional study. *Gynecol Oncol*. Published online June 3, 2014.
471 doi:10.1016/j.ygyno.2014.05.026
- 472 14. Haguenoer K, Sengchanh S, Gaudy-Graffin C, et al. Vaginal self-sampling is a cost-
473 effective way to increase participation in a cervical cancer screening programme: a
474 randomised trial. *Br J Cancer*. 2014;111(11):2187-2196. doi:10.1038/bjc.2014.510
- 475 15. French National Authority for Health. [*Follow-up guidelines for a patient with an*
476 *abnormal Pap smear test result. 2002 updated data.*]; 2002.
- 477 16. Hesselink AT, Meijer CJLM, Poljak M, et al. Clinical validation of the Abbott RealTime
478 High Risk HPV assay according to the guidelines for human papillomavirus DNA test
479 requirements for cervical screening. *J Clin Microbiol*. 2013;51(7):2409-2410.
480 doi:10.1128/JCM.00633-13
- 481 17. Park Y, Lee E, Choi J, Jeong S, Kim HS. Comparison of the Abbott RealTime High-
482 Risk Human Papillomavirus (HPV), Roche Cobas HPV, and Hybrid Capture 2 Assays to
483 Direct Sequencing and Genotyping of HPV DNA. *J Clin Microbiol*. 2012;50(7):2359-
484 2365. doi:10.1128/JCM.00337-12
- 485 18. Nayar R, Wilbur DC. The Pap test and Bethesda 2014. *Cancer Cytopathol*.
486 2015;123(5):271-281. doi:10.1002/cncy.21521
- 487 19. Eldridge SM, Ashby D, Kerry S. Sample size for cluster randomized trials: effect of
488 coefficient of variation of cluster size and analysis method. *Int J Epidemiol*.
489 2006;35(5):1292-1300. doi:10.1093/ije/dyl129
- 490 20. Morikawa T, Yoshida M. A useful testing strategy in phase III trials: combined test of
491 superiority and test of equivalence. *J Biopharm Stat*. 1995;5(3):297-306.
492 doi:10.1080/10543409508835115
- 493 21. Zou G, Donner A. Confidence interval estimation of the intraclass correlation coefficient
494 for binary outcome data. *Biometrics*. 2004;60(3):807-811. doi:10.1111/j.0006-
495 341X.2004.00232.x
- 496 22. Giorgi Rossi P, Fortunato C, Barbarino P, et al. Self-sampling to increase participation in
497 cervical cancer screening: an RCT comparing home mailing, distribution in pharmacies,
498 and recall letter. *Br J Cancer*. 2015;112(4):667-675. doi:10.1038/bjc.2015.11
- 499 23. Malone C, Barnabas RV, Buist DSM, Tiro JA, Winer RL. Cost-effectiveness studies of
500 HPV self-sampling: A systematic review. *Prev Med*. Published online January 3,
501 2020:105953. doi:10.1016/j.ypped.2019.105953
- 502 24. Ketelaars PJW, Bosgraaf RP, Siebers AG, et al. High-risk human papillomavirus
503 detection in self-sampling compared to physician-taken smear in a responder population
504 of the Dutch cervical screening: Results of the VERA study. *Prev Med*. 2017;101:96-
505 101. doi:10.1016/j.ypped.2017.05.021

- 506 25. Smith M, Lew JB, Simms K, Canfell K. Impact of HPV sample self-collection for
507 underscreened women in the renewed Cervical Screening Program. *Med J Aust.*
508 2016;204(5):1941e-19417. doi:10.5694/mja15.00912
- 509 26. French National Authority for Health. [Evaluation of Papillomavirus research (HPV) in
510 cervical precancerous and cancerous lesions primary screening and the place of double
511 immunostaining p16 / Ki67]. Published online July 10, 2019.
- 512

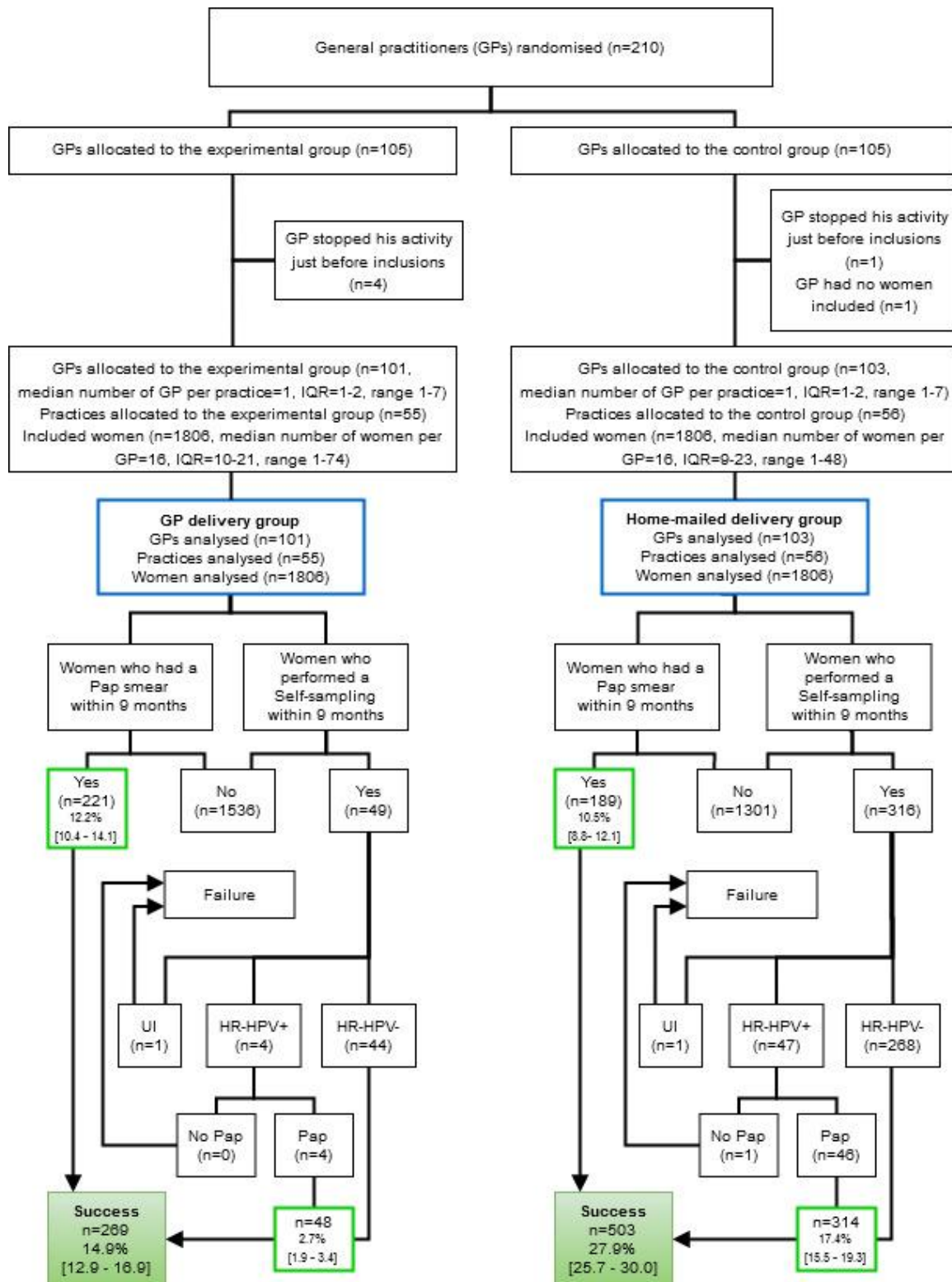
513 **Figures titles and footnotes**

514 **Figure 1: Timeline and blinding status of the cluster randomized trial process**



- 1 Information**
All GPs and gynaecologists practicing in Indre-et-Loire received a letter describing the two delivery strategies.
- 2 Identification and inclusion**
All the 527 GPs practicing in Indre-et-Loire were identified and a random sample of 210 GPs was drawn from this population.
- 3 Randomisation**
A computer-generated allocation sequence with a 1:1 ratio, stratified on the practice size according to 5 strata was performed by an independent statistician.
- 4a Kit delivery at GP**
GPs in the GP delivery group received 15 vaginal self-sampling kits with delivery instructions at their practice. They were not aware of the study hypotheses.
- 4b No information**
GPs assigned in the home-mailed group received no further information. They were not aware of the study hypotheses.
- 5 Identification and inclusion**
Women meeting inclusion criteria were identified with blinding in the Cancer Screening Department database and the first 1806 eligible women in each group were included. Women were informed in the reminder letter that the screening proposition was part of a behavioral study but there was no participant consent.
- 6a Intervention delivery**
In the GP delivery group, women received a reminder letter inviting them to consult their referring GP to collect a vaginal self-sampling kit. Women knew they were participating in a study but were not aware of the study hypotheses, especially the two interventions compared.
- 6b Intervention delivery**
In the home-mailed delivery group, women received a reminder letter with a vaginal self-sampling kit directly at home. Women knew they were participating in a study but were not aware of the study hypotheses, especially the two interventions compared.
- 7 Outcome assessment**
Participation in complete cervical cancer screening within 9 months following the reminder letter to women was evaluated according to self-sampling results, received from a blinded central laboratory and Pap smear results, extracted from routinely collected data. Women knew they were participating in a study but were not aware of the study hypotheses, especially the outcome.

516 **Figure 2:** Study flow chart and results.



517
 518 Abbreviations: HR-HPV+, positive for high-risk HPV; HR-HPV-, negative for high-risk
 519 HPV; UI, uninterpretable HPV test result; IQR, interquartile range; GP, general practitioner;
 520 PAP, Papanicolaou cytology. 95% confidence intervals are presented in brackets

521 **Tables and footnotes**

Table 1. Participation in complete cervical cancer screening (CCS) within 9 months after sending reminder letters, by trial group				
	GP delivery (n=1806)	Home-mailed delivery (n=1806)	Absolute difference in percentage points (95% CI)	P value ^a
	n (% [95% CI]) ICC (95% CI)			
Total complete participation (by self- sampling or Pap smear)	269 (14.9% [12.9 to 16.9]) 0.021 (0.001 to 0.220)	503 (27.9% [25.7 to 30.0]) 0.004 (0.002 to 0.098)	-13.0 (-15.9 to -10.0)	<0.001
Complete participation by self- sampling	48 (2.7% [1.9 to 3.4]) 0.012 (0.000 to 0.519)	314 (17.4% [15.5 to 19.3]) 0.011 (0.000 to 0.171)	-14.7 (-16.7 to -12.7)	<0.001
Complete participation by Pap smear	221 (12.2% [10.4 to 14.1]) 0.022 (0.001 to 0.254)	189 (10.5% [8.8 to 12.1]) 0.018 (0.000 to 0.263)	1.8 (- 0.7 to 4.3)	0.13

522 ICC = intraclass correlation coefficient

523 ^ap values were obtained from a ratio estimator approach based on the standard Pearson chi-

524 square statistic with adjustment for clustering

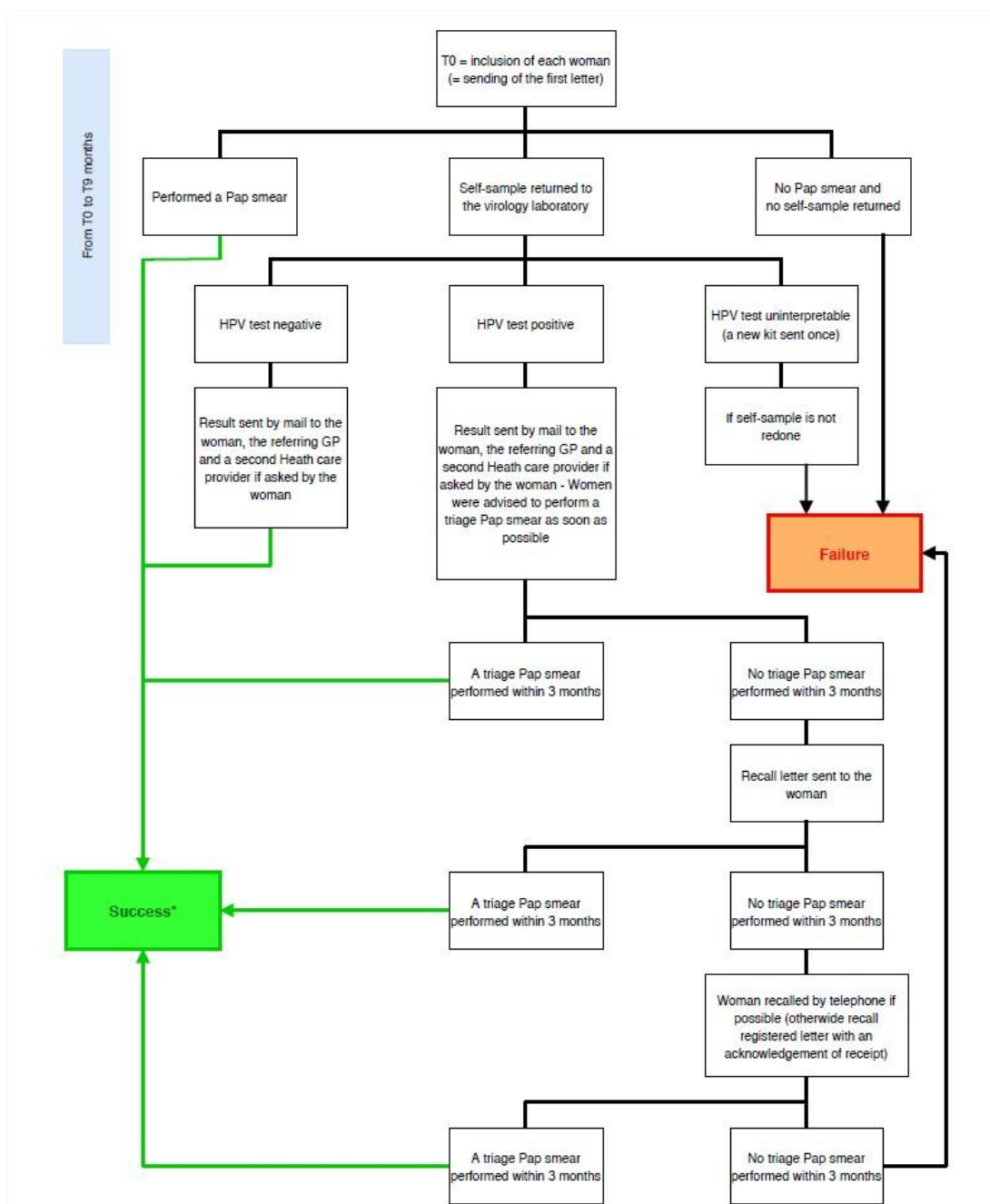
Table 2: Cost-effectiveness results			
	GP delivery	Home-mailed delivery	
Base-case results			
Number of women included	1806	1806	
Participation rate	0.149	0.279	
Total cost	16 272.06 €	28 173.60 €	
Mean cost per women included	9.01€	15.60€	
Cost-effectiveness ratio	60.52€	56.00€	
Incremental cost-effectiveness ratio (ICER) per extra-screened woman	Ref.	50.81€	
Sensitivity analysis (ICER per extra-screened woman)			
Cost of home-mailed delivery kit = 5.00€ (1.559€ ^a)	Ref.	77.36€	
Cost of HR-HPV test and mailing of results = 20.00€ (37.80€ ^a)	Ref.	30.57€	
Probability of returning the test within 9 months in the GP delivery group = 5.43% (2.71 ^a)	Ref.	45.93€	
Cost of the GP's consultation + sending the kit to the GP = 26.6438€ (24.6438€ ^a)	Ref.	50.39€	
Proportion of Pap smears performed with and without fee overruns	Pap smear taking = 0.00 (0.45 ^a)	Ref.	50.42€
	Pas smear analysis = 0.00 (0.25 ^a)	Ref.	50.70€
Pap smear analysis (cytology analysis) and results sending without extra fees = 20€ (15.40€ ^a)	Ref.	50.95€	

525 ^abase value

526 **Appendix Material**

527
 528 Leaflet explaining how to perform the vaginal self-sampling (designed in collaboration with a
 529 medical illustrator)

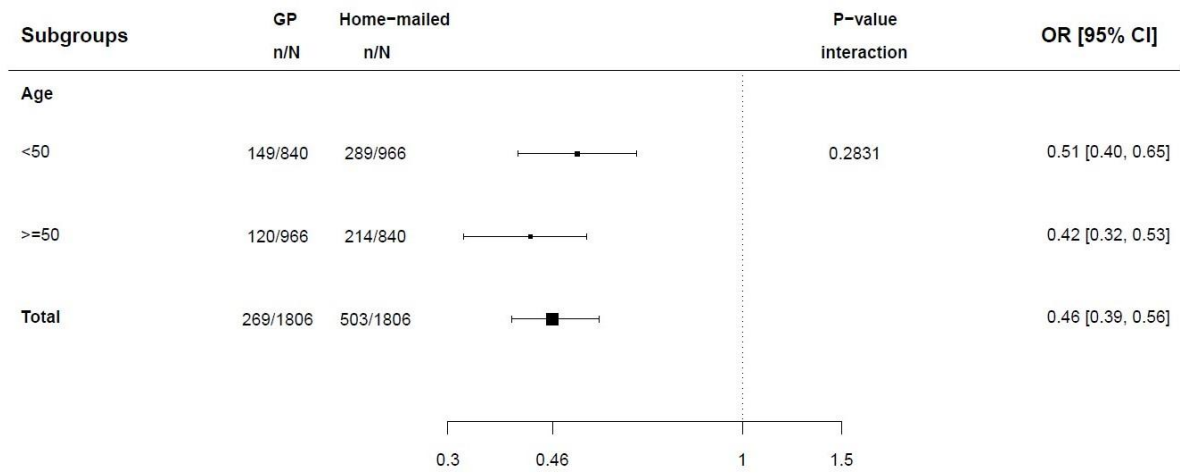
530
 531 **Figure S1:** Procedures for screening both intervention groups and definition of complete
 532 screening.



533

534 **Figure S2:** Sub-group analyses.

535 The group*age interaction was not statistically significant ($p = 0.2831$).



536

537 **Table S1:** Pap smear results by trial group and type of participation among women who participated in complete Cervical Cancer screening
 538 (CCS) within 9 months after reminder letters were sent

Table S1. Pap smear results by trial group and type of participation among women who participated in complete cervical cancer screening (CCS) within 9 months after reminder letters were sent									
Pap smear results	Intervention group						Total		
	GP delivery group			Home-mailed delivery group			Screening Pap smear	Triage Pap smear	Total
	Screening Pap smear (N=221)	Triage Pap smear (N=4)	Total (N=225)	Screening Pap smear (N=189)	Triage Pap smear (N=46) ^a	Total (N=235)	Screening Pap smear (N=410)	Triage Pap smear (N=50) ^a	Total (N=460)
Unknown result ^b	14 (6.3%)	–	14 (6.2%)	24 (12.7%)	2 (4.3%)	26 (11.1%)	38 (9.3%)	2 (4.0%)	40 (8.7%)
Known result ^c	207 (93.7%)	4 (100%)	211 (93.8%)	165 (87.3%)	44 (95.7%)	209 (88.9%)	372 (90.7%)	48 (96.0%)	420 (91.3%)
Normal	203 (98.1%)	3 (75%)	206 (97.6%)	159 (96.4%)	39 (88.6%)	198 (94.7%)	362 (97.3%)	42 (87.5%)	404 (96.2%)
Abnormal	4 (1.9%)	1 (25%)	5 (2.4%)	6 (3.6%)	5 (11.4%)	11 (5.3%)	10 (2.7%)	6 (12.5%)	16 (3.8%)
ASC-US	2 (0.9%)	–	2 (0.9%)	6 (3.6%)	3 (6.8%)	9 (4.3%)	8 (2.1%)	3 (6.2%)	11 (2.6%)
ASC-H	–	–	–	–	1 (2.3%)	1 (0.5%)	–	1 (2.1%)	1 (0.2%)
LSIL	1 (0.5%)	1 (25%)	2 (0.9%)	–	–	–	1 (0.3%)	1 (2.1%)	2 (0.5%)
HSIL	1 (0.5%)	–	1 (0.5%)	–	1 (2.3%)	1 (0.5%)	1 (0.3%)	1 (2.1%)	2 (0.5%)
AGC	–	–	–	–	–	–	–	–	–

Abbreviations: AGC, atypical squamous cells; ASC-H, atypical squamous cells, cannot rule high-grade lesion; ASC-US, atypical squamous cells of undetermined significance; HSIL, high-grade squamous intraepithelial lesions; LSIL, low-grade squamous intraepithelial lesions. Data are number of samples.

^a Among the 47 women with a positive HR-HPV test result on the vaginal self-sampling, 1 did not have the recommended triage Pap smear

^b the date for the Pap smear was known but not the cytology result

^c According to the 2001 Bethesda system

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540

541 **Table S2:** Costs of resources engaged per screened women for each intervention group

Table S2: Costs of resources engaged per screened women for each intervention group				
Cost items		GP delivery group	Home-mailed delivery group	Base value
Sending of the reminder letter inviting women to consult their referring GP to collect a vaginal self-sampling kit ^a		X		0.436€
GP's consultation + sending the kit to the GP ^b		X		24.6438€
Home-mailed delivery: sending of the reminder letter containing the vaginal self-sampling kit directly at home ^c			X	1.559€
Return of the self-sampling to the centralised laboratory ^d		X	X	1.50€
HR-HPV test and mailing of results sending ^e		X	X	37.80€
Sending of a second self-sampling kit, if the first self-sampling is uninterpretable ^f		X	X	3.699€
Reminder letter and phone call after a positive HR-HPV result on the vaginal self-sampling without triage Pap smear	reminder letter 1 ^g	X	X	0.748€
	reminder letter 2 ^h	X	X	5.138€
	reminder phone call 2 ⁱ	X	X	5.00€
Consultation to perform a pap smear (general practitioner, midwife or gynaecologist) including potential extra fees ^j	by a gynaecologist with extra fees	X	X	48.00€
	by a gynaecologist without extra fees	X	X	28.00€
	by a general practitioner	X	X	27.82€
	by a midwife	X	X	21.76€
Pap smear analysis (cytology analysis) and result sending	with extra fees	X	X	25.00€
	without extra fees	X	X	15.40€
^a Envelope, letterhead paper, printing and postal fee				
^b GP consultation + kit: envelope, self-sampling device, leaflet, resealable zipper bag, identification sheet, return envelope and postal fee for each kit				
^c Envelope, letterhead paper, printing and postal fee, self-sampling device, leaflet, resealable zipper bag, identification sheet, return envelope				
^d Postal fee for sampling return				
^e HR-HPV test analysis and sending the result				
^f Special envelope for individual sending, letterhead paper, printing and special postal fee for individual sending, self-sampling device, leaflet, resealable zipper bag, identification sheet, return envelope				
^g Envelope, letterhead paper, printing and postal fee				
^h Envelope, letterhead paper, printing and special postal fee for registered letter with acknowledgement of receipt				
ⁱ Cancer screening department staff time				
^j Consultation with a healthcare professional to perform a Pap smear				
^k In France, the GP consultation cost increased from 23€ to 25€ on May 1, 2017.				

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543

544 **Table S3:** Model data for cost-effectiveness sensitivity analyses

Table S3: Model data for cost-effectiveness sensitivity analyses				
		Low value	Base value	High value
Cost of home-mailed delivery: sending of the reminder letter containing the vaginal self-sampling kit directly at home			1.559€	5.00€
Costs of HR-HPV test and mailing of result		20.00€	37.80€	
Probability of returning the self-sampling within 9 months in the GP delivery group			2.71%	5.43%
Cost of GP's consultation + sending the kit to the GP			24.6438€	26.6438€ ^a
Proportion of pap smears performed with and without fee overruns	Pap smear taking	0.00	45%	
	Pap smear analysis	0.00	25%	
Cost of pap smear analysis (cytology analysis) and result sending	without extra fees		15.40€	20.00€
a In France, the GP consultation cost increased from 23€ to 25€ on May 1, 2017.				

545